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(54) Title: BIOLOGICAL AGENTS OF INCREASED EFFICACY

(57) Abstract

Method for rendering normally insoluble biologically active materials, such as the substituted guanidine compounds soluble in plant tissue by combining said active material with a metal chelate. The method allows the active material to be formulated for liquid or granule application. The compounds proposed by the invention comprise the active material combined with a metal chelate, preferably Copper E.D.T.A. and one preferred compound comprises the 2 - Guanidinododecane acetate combined with Copper E.D.T.A.

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Biological agents of increased efficacy

DESCRIPTION

The present invention relates to compounds, being biologically active compounds, of increased efficacy and to a method of preparing same.

In the agricultural/horticultural arts there are two
5 basic types of compounds.

(1) "Soluble" compounds which can be taken into the plant tissue and

(2) "Non-soluble" compounds which cannot be taken into the plant tissue.

10 The "non-soluble" compounds can only be applied to external surfaces of the plant or the surrounding soil and, as such, can only protect the plant against external attack by certain diseases or when the disease causes some breakdown of the external surface of the plant, for example surface dis-
15 ruptions such as scabs. A further disadvantage of surface applied compounds is that, being exposed to the elements, they have a limited life and successive applications may be necessary to continue the protection of the plant.

The "soluble" compounds, which may be translocated or
20 more advantageously systemic, are most advantageous because being within the plant tissue they can make the plant resistant to disease and their effective life can be far longer than non-soluble compounds.

In this specification "plant tissue" means any plant tissue
25 including seed, growing plant, or harvested crop where the tissue is still active and capable of translocation or systemic movement of matter within said tissue.

The present invention seeks to provide a method by which certain normally non-soluble compounds can be rendered soluble
30 in plant tissue and to compounds rendered soluble in plant tissue



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by said method.

According to the present invention there is provided a method for rendering a normally insoluble biologically active material soluble in plant tissue comprising the steps of combining said active material with a metal chelate.

The invention thus solves the above problem by recognising that certain normally non-soluble biologically active materials can be combined with a metal chelate. When such an active material is combined with a metal chelate the compound is rendered soluble in plant tissue.

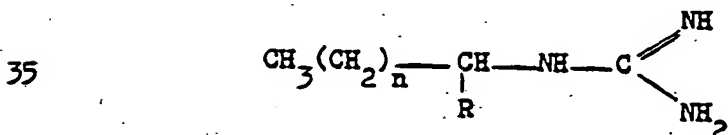
In one embodiment in accordance with the invention the method includes the step of mixing said active material with a dispersing agent before adding the metal chelate.

Preferably water is added to the active material/dispersing agent mixture before the metal chelate is added to said mixture and the aqueous formulation, including the metal chelate is agitated until an intimate mixture has been obtained, generally indicated when the formulation becomes clear, and at which stage the formulation is relatively stable between - 5°C and 80°C.

Formulations prepared by this method can be readily diluted with water for application to the plant tissue by any conventional means for liquid treatment, for example, by conventional spraying when the dispersing agent assist wetting of the plant tissue.

In an alternative method in accordance with the invention the active material and the metal chelate are dissolved in a hot solvent. By this method the solvent, with the dissolved active material and metal chelate, may be applied to a granule to obtain release of the active material to the plant tissue over a period of time.

It has been found that a most convenient active material for producing the invention comprises biologically active material of the general formula:-



in which n is an interger of 7 to 11 and R is methyl or ethyl



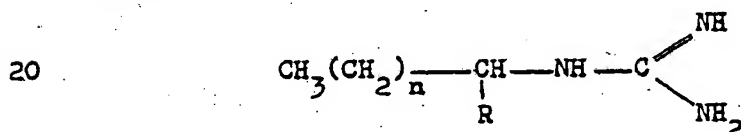
and in a preferred embodiment of the invention said active material is combined with with copper E.D.T.A.

The invention also envisages a soluble, biologically active compound comprising a normally insoluble biologically active material combined with a metal chelate.

The metal chelate may comprise iron, manganese or zinc but for many compounds the metal chelate preferably comprises copper E.D.T.A.

Compounds which may be combined with metal chelates and which are of particular value are dodine and the substituted guanide compounds, both of which are well known non-soluble compounds, the latter being known to be useful for controlling fruit tree fungi and for protecting potatoes against fungal and bacterial attack, for example "late blight" to which potatoes are susceptible.

Compounds of particular importance in practising the present invention are the 2 - guanidino alkanes of the following general formula:-



in which n is an integer of 7 to 11 and R is methyl or ethyl, which have outstanding utility in protecting potatoes from late blight while showing a very low order of phytotoxicity. A compound of this general formula which is preferred is 2 - guanidino-n-dodecane.

When a substituted guanidine compound is to be combined with a metal chelate in accordance with the invention, the compound may be used in the form of a salt formed with an acid. The acetate is presently preferred although the phosphate may efficaciously be used.

The present invention will now be illustrated by reference to the following examples:-

Example 1. An aqueous formulation was prepared as follows:-

10 g of Guanidinododecane acetate and, as a dispersing agent, 10 g of Nonylphenoxyethyleneoxyethanol, were made up to 100 m. with water. To this was added 10 grms. of copper E.D.T.A. and the mixture was agitated until an aqueous solution stable at temperatures ranging from - 5°C to 80°C was produced. This



material may be applied after suitable dilution in water to constitute 1/100th to 1/500th of the total volume and applied by standard spraying equipment to crops in the field or under glass. The dosage rate required in most agricultural and horticultural crops lies between 0.1 and 5 kilos per hectare; this dosage being based on the weight of Guanidino-dodecane applied.

When the application was made to vines, good control of *Aspergillus niger* and *Penicillium expansum* was obtained.

The combination of the 2 - guanidinododecane with Copper E.D.T.A. has also proved effective in the control of soil pathogens and an advantageous formulation for this purpose is illustrated in the following example.

Example 2. 5 grms. Copper E.D.T.A. with,

5 grms. 2 - Guanidinododecane acetate is dissolved in a hot solvent comprising polyethyleneglycol, the amount required being within 25 to 30 ml. This formulation was then applied to diatomaceous earth of a particle size described as 20 - 40 mesh.

The quantity of granules here is 950 grms, and to this are added 10 grms. chalk and 5 grms. of starch. This encapsulates the active material within and on the granule and delays its release. These granules contain 0.5% of Guanidinododecane and 0.5% Copper E.D.T.A.

These granules when applied to soil, for slow release to the surrounding crop, at the rate of 100 kilos per hectare will effectively control *Pythium ultimum* and *Rhizoctonia* spp.

The above formulations have value in the control of bacterial pathogens *Erwinia caratovera* var *atroseptica*, *Erwinia carotovera* var *carotovera* and *Erwinia caratovera* var *chrysanthemi*.

It will be appreciated that when the compounds proposed by the invention are applied to granules there is a release of said material over a period of time and the plant tissue will thereby be dosed with the active material over the release period from the granules.

Whilst compounds proposed by present invention can provide

ORIGINAL

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internal, mobile plant protection agents such as insecticides, fungicides and bacteriocides during the growth of the plant. startling results are obtained when said compounds are applied to certain fruits, vegetables, and flowers immediately before or after harvesting or cutting when the active compounds delay maturing of the crop and afford protection against external and internal decay and rot mechanisms.

By way of example, when lettuce was sprayed with the compounds a short time before being harvested the harvested lettuce treated with the compounds remained in good saleable condition and edible for many days after untreated lettuce, harvested at the same time, had become inedible.

In like manner flowers treated with the compounds before cutting remained in good order long after untreated flowers had become necrotic.

Further, when untreated flowers were arranged with their stems in water dosed with the compounds proposed by the invention, the compounds gave protection against decay and rot and delayed maturing such that the flowers remained in good order for up to a week whilst flowers in untreated water became unsightly in two to three days.

The invention will now be described further by way of trials carried out on potatoes.

A. Chemical control of a tuber born disease is achieved by various methods and chemicals, the most common of which known to the art employ tecnazene, thiabendazole or 2 - amino butane. Application of the formulation are made by fumigation (Graham and Hamilton 1970) by low volume mist application (Logan et al 1975) or in the case of tecnazene by hand.

Although effective control of some diseases is obtained by the use of these compounds *Spongospora subterranea* and to a lesser extent *Rhizoctonia solani* are not significantly reduced.

The trials now to be described used, as the active material;

B. Chemical name: 2 - Guanidinododecane acetate

Molecular formula: $C_{15}H_{33}O_2N_3$

Structural formula: $CH_3 \cdot (CH_2)_9 \cdot CH \cdot CH_3$
 $\begin{array}{c} \text{NH} \\ \diagup \\ \text{NH} - C = \text{NH} \\ \diagdown \\ \text{NH}_2 \end{array}$

$CH_3 COOH$



Molecular weight: 287.45

Description: Colourless crystals

Solubility: In water, at 20°C 2.2 mg/ml
at 80°C 100 mg/ml

Melting Point: 150°C

Stability: Indefinitely stable at temperatures below the melting point. Under strongly alkaline conditions the free base is formed; this is thermally unstable, evolving ammonia at 60°C

C. Toxicology:

Acute studies	Technical	10% formulation
Oral, rat, LD/50	1.17 gm/kg	9.48 gms/kg
Intra peritoneal, rat		
LD/50	20.7 mg/kg	-

Spectrum of activity:

"in vivo/ test procedures had demonstrated fungicidal activity against the following pathogens:

Helminthosporium solani; *Phoma exigua* var *foveata*
Rhizoctonia solani; *Spongospora subteranea*.

The active material was mixed with Copper E.D.T.A. in identical manner to that described for example 1 and diluted to give two different concentrations of the 2 - Guanidinododecane acetate, one of 1% and the other of 2%.

Application of the active material as a water soluble formulation had to be made as a mist treatment and, for this purpose, a standard rotary disc low volume applicator was mounted over a roller conveyor and calibrated to give an output of 2.0 litres per hour with a droplet size of circa 70 microns.

The roller conveyor had a variable speed drive with a maximum throughput of 2 tonnes per hour. Potato tubers were treated in 50 kgs. batches and stored in trays containing 10 kgs.

Seed potato tubers of the cultivar Maris Bard were selected due to the high incidence of *Rhizoctonia solani* and *Spongospora subterranea*.

The disease level in the tubers to be used in each trial was assessed by taking 5 by 10 kg samples at random from a 500 kg. box. These were sub-sampled twice to give two 25 tuber samples



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which were assessed on the 0 - 5 scale for *Rhizoctonia solani*, *Spongospora subterranea* and *Helminthosporium solani* where 1 = 5% cover; 2 = 5 to 10% cover; 3 = 10 to 25% cover; 4 = 25 to 50% cover; 5 = 50% cover. Both concentrations of active material were used and, by controlling the throughput of potatoes at 16.6 kg/minute, two volume rates could be compared.

The trials included 4 blanks within each trial, two were misted with water plus the non-ionic solubilising agent from the active material formulation and two which had been conveyed through the equipment without any mist application.

Details of the treatments are given in Table 1 and the disease scores in Table 2 for tuber stocks used in trials.

TABLE 1

% a.i. Active Material	Flow rate Mister	Flow rate Conveyor	Volume/ tonne	Theoretical application
1.0%	2 l/hour	2 tonnes/hr	1 litre	10.0 p.p.m.
1.0%	2 l/hour	1 tonne/hour	2 litres	20.0 p.p.m.
2.0%	2 l/hour	2 tonnes/hr	1 litre	20.0 p.p.m.
2.0%	2 l/hour	1 tonne/hr	2 litres	20.0 p.p.m.

Residue estimations were carried out on samples of tubers following treatment and these are reported in Table 4.

TABLE 2

Stock	<i>Rhizoctonia solani</i>	Disease Score <i>Spongospora subterranea</i>	<i>Helminthosporium solani</i>
A	3	2	1
B	5	1	1
C	2	4	0
D	2	5	0

Phoma exigua var *foveata* was estimated following storage two weeks before planting.

RESULTS

Following treatment the tubers were stored at 5°C and 92 Rh so as to give favourable conditions for disease development yet realistic as far as some commercial storage systems are



concerned. Between 100 and 120 days after treatment the stocks were assessed for gangrene, dry rot and silver scurf. These results are given in Table 3.

TABLE 3

5	Stock	Treatment	% Disease Control/Score	
			Phoma	Helminthosporium
10	A	1 litre/tonne of 1.0%	67.6	2
	A	1 litre/tonne of 2.0%	91.2	1
	A	2 litre/tonne of 1.0%	85.3	1
	A	2 litre/tonne of 2.0%	97.0	1
	A	None	0(34%)	(3)
	A	Water & Dispersant	8.8	(2)
	B	1 litre/tonne of 1.0%	65.5	2
	B	1 litre/tonne of 2.0%	93.1	1
	15 B	2 litre/tonne of 1.0%	82.7	1
	B	2 litre/tonne of 2.0%	93.1	1
20	B	None	0(29%)	2
	B	Water & Dispersant	3.4	2

() = % phoma

20 Disease control is expressed as a percentage using the formula:

$$\frac{\text{Control infection\%} - \text{Treated infection\%}}{\text{Control infection\%}} \times 100$$

25 In order to relate the level of disease control to the quantity of active material residue determinations were carried out on representative samples twenty four hours after application, these results are given in Table 4.

TABLE 4

30	% ai. Active Material	Volume/ tonne	Theoretical dosage	Actual dosage
	1.0%	1 litre	10 p.p.m.	7.3 p.p.m.
	1.0%	2 litres	20 p.p.m.	16.1 p.p.m.
	2.0%	1 litre	20 p.p.m.	13.4 p.p.m.
	2.0%	2 litres	40 p.p.m.	31.7 p.p.m.

Similar results were obtained from the other stocks of tubers for the control of gangrene during storage.

Planting of treated and untreated seed in replicated blocks situated on low lying sandy loam occurred between 130 and 150 days after treatment.

During the growing season, plant emergence stem number and disease levels were assessed. Plots were harvested 120 days after planting and at that time the progeny tubers were graded and examined for black scurf and powdery scab.

There was an overall reduction in the incidence of both of these diseases. Symptoms of silver scurf were not evident at the time of grading in either the treated or untreated stocks.

Both average tuber weight and total plant yields were higher in the stocks treated with active material but the control of *spongospora subterranea* would increase the marketable yield of tubers from the misted stocks.

The results of the various treatments on disease levels both in the crop and in the progeny tubers are given in Table 5.

TABLE 5

20	Stock	Treatment volume/ cone/Tonne	R.solani Stem	% Disease reduction	
				Tubers	S.Subterranea Tubers
25	A	1 litre 1.0%	52.7	64.2	14.2
	B		57.1	45.7	-
	C		75.0	-	37.8
	D		69.2	-	31.1
25	A	2 litre 1.0%	58.3	92.5	100.0
	B		88.6	88.5	-
	C		91.6	-	81.0
	D		92.3	-	91.1
30	A	1 litre 2.0%	86.1	77.7	85.7
	B		79.5	88.5	-
	C		91.6	-	83.7
	D		84.6	-	88.8
	A	2 litres 2.0%	100.0	100.0	100.0



TABLE 5 (continued)

Stock	Treatment Volume/ cone/Tonne	R.solani Stem	% Disease reduction	
			Tubers	S.Subterranea Tubers
B		95.5	97.1	-
C		100.0	-	100.0
D		100.0	-	97.7
% infection				
A	2 litres water	38	14	7
B		44	32	2
C		14	4	31
D		10	5	42
A	None	36	27	7
B		49	35	0
C		12	3	37
D		13	1	45

It should be observed from the test results that whilst both *Rhizoctonia solani* and *Spongospora subterranea* are soil inhabiting and possess alternative hosts, reduction of seed infection appears to reduce the incidence in the progeny tubers. The application of the active material as a low volume mist during the storage period reduces the amount of disease in the growing crop and in the progeny tubers. At this stage it is not clear as to the disease control spectrum but the ability of the active material to penetrate the protective systems enjoyed by the pathogens *Rhizoctonia solani* and *Spongospora subterranea* is a major advance on current commercial practice.

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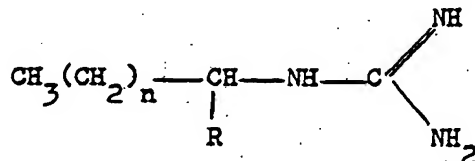
Agents for the Applicants.



CLAIMS

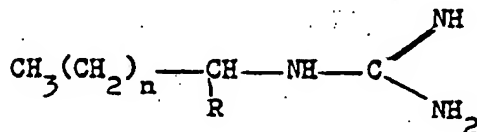
1. A method for rendering a normally insoluble, biologically active material soluble in plant tissue comprising the steps of combining said active material with a metal chelate.
- 5 2. A method as claimed in Claim 1 comprising the steps of mixing said active material with a dispersing agent before adding the metal chelate.
3. A method as claimed in Claim 1 comprising the steps of adding water to the active material and dispersing agent before
10 adding the metal chelate, and agitating the aqueous formulation until a clear solution is obtained.
4. A method as claimed in Claim 1 and wherein the weight of metal chelate is equal to the weight of active material.
5. A method as claimed in Claim 1 including the steps of
15 dissolving the active material and the metal chelate in a hot solvent and applying the solvent to a granule of diatomaceous earth.
6. A method for rendering a biologically active material of the general formula:-

20



- 25 in which n is an integer of 7 to 11 and R is methyl or ethyl, soluble in plant tissue comprising the step of combining said active material with copper E.D.T.A.
7. A soluble, biologically active compound comprising a normally insoluble biologically active material combined with a metal chelate.
- 30 8. A compound as claimed in Claim 7, in which the active compound comprises a substituted guanide compound.
9. A compound as claimed in Claim 7 in which the active compound is of the general formula:-

35



in which n is an integer of 7 to 11 and R is methyl or ethyl.

10. A compound as claimed in Claim 7, in which the active material comprises 2 Guanidinododecane acetate.
11. A compound as claimed in Claim 7, in which the metal chelate
5 comprises iron, manganese, zinc or copper E.D.T.A.
12. A compound as claimed in Claim 7, comprising equal parts by weight of the biologically active material and the metal chelate.
13. A compound as claimed in Claim 7, comprising the biologically active material, the metal chelate, and a dispersing agent.
- 10 14. A compound as claimed in Claim 13, in which the dispersing agent comprises Nonylphenoxyethyleneoxyethanol.
15. A compound as claimed in Claim 7, in which the biologically active material and the metal chelate are dissolved in a solvent.
16. A compound as claimed in Claim 15, in which the solvent com-
15 prises polyethyleneglycol.



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 83/00259

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ³ : A 01 N 61/00; A 01 N 47/44; A 01 N 37/44																										
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched ⁴</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border: 1px solid black; text-align: left;">Classification System</th> <th style="border: 1px solid black; text-align: left;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">IPC³</td> <td style="border: 1px solid black; padding: 5px;">A 01 N</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched ⁵</div>			Classification System	Classification Symbols	IPC ³	A 01 N																				
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; border: 1px solid black;">Category ⁶</th> <th style="border: 1px solid black;">Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷</th> <th style="width: 15%; border: 1px solid black;">Relevant to Claim No. ¹⁸</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="padding: 5px;">GB, A, 1445074 (PETI NITROGENMUVEK) 4 August 1976 see claims; page 2, lines 21-49; page 4, lines 17-29 ---</td> <td style="text-align: center; vertical-align: top;">1,4,7,11-13</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="padding: 5px;">FR, A, 1578111 (C. LOUVET) 14 August 1969 see page 2, lines 20-25 and page 1, lines 11-30 ---</td> <td style="text-align: center; vertical-align: top;">1-3,7,11,13</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="padding: 5px;">FR, A, 2335153 (SAININ) 15 July 1977 see claim 1; page 2, line 20 - page 5, line 10 ---</td> <td style="text-align: center; vertical-align: top;">1,7,11,13</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="padding: 5px;">GB, A, 1476728 (RECKITT & COLMAN PROD.) 16 June 1977 ---</td> <td style="text-align: center; vertical-align: top;">6,9,10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="padding: 5px;">GB, A, 1476729 (RECKITT & COLMAN PROD.) 16 June 1977 ---</td> <td style="text-align: center; vertical-align: top;">6,9,10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="padding: 5px;">FR, A, 1130117 (PECHINEY) 31 January 1957 ---</td> <td style="text-align: center; vertical-align: top;">1,7</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="padding: 5px;">FR, A, 2322545 (R. COUDRAY) 1 April 1977 -----</td> <td style="text-align: center; vertical-align: top;">1</td> </tr> </tbody> </table>			Category ⁶	Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸	X	GB, A, 1445074 (PETI NITROGENMUVEK) 4 August 1976 see claims; page 2, lines 21-49; page 4, lines 17-29 ---	1,4,7,11-13	X	FR, A, 1578111 (C. LOUVET) 14 August 1969 see page 2, lines 20-25 and page 1, lines 11-30 ---	1-3,7,11,13	X	FR, A, 2335153 (SAININ) 15 July 1977 see claim 1; page 2, line 20 - page 5, line 10 ---	1,7,11,13	A	GB, A, 1476728 (RECKITT & COLMAN PROD.) 16 June 1977 ---	6,9,10	A	GB, A, 1476729 (RECKITT & COLMAN PROD.) 16 June 1977 ---	6,9,10	A	FR, A, 1130117 (PECHINEY) 31 January 1957 ---	1,7	A	FR, A, 2322545 (R. COUDRAY) 1 April 1977 -----	1
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁶ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance.</p> <p>"E" earlier document but published on or after the international filing date.</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </div> </div>																										
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search ¹⁹ <div style="text-align: center;">27th January 1984</div> </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report ²⁰ <div style="text-align: center; font-size: 1.2em;">15 FEB. 1984</div> </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority ¹ <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer ²⁰ <div style="text-align: right;"> G.L.M. Kruenberg </div> </td> </tr> </table>			Date of the Actual Completion of the International Search ¹⁹ <div style="text-align: center;">27th January 1984</div>	Date of Mailing of this International Search Report ²⁰ <div style="text-align: center; font-size: 1.2em;">15 FEB. 1984</div>	International Searching Authority ¹ <div style="text-align: center;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer ²⁰ <div style="text-align: right;"> G.L.M. Kruenberg </div>																				
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 83/00259 (SA 5935)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/02/84

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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FR-A- 2322545	01/04/77	None	

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